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Treatment of older adults with acute myeloid leukemia: state of the art and current perspectives

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Acute myeloid leukemia (AML) is a disease of older adults, with a median age at diagnosis of 67 years in the United States. Decisions regarding the aggressiveness and timeliness of therapy are challenging in older adults, as the disease biology predicts for chemotherapy resistance, and intensive therapy is accompanied by high treatment-related mortality. In older patients, complete remission rates to standard remission induction therapy range from 40-60%, with limited long-term survival. Newer treatments are less-aggressive, with the promise of near-comparable response rates to standard cytotoxic therapy. Clinical trials should be considered at every stage of treatment in this group of patients.

Why focus on older adults with acute myeloid leukemia?

Epidemiology

AML is the most common leukemia subtype, with an estimated 13,000 new diagnoses yearly in the USA.[1] It is also a disease of older adults, commonly defined as people > 60 years of age, with a median age at diagnosis of 67 years.[2] This translates to a yearly incidence of new AML diagnoses in the USA of 17.6/100,000 for people 65 years of age or older, compared to 1.8/100,000 for people <65 years. Worldwide, the incidence of AML in older adults is increasing, likely due to the effects of environmental exposures during an industrial age, the late effects of chemotherapy and radiation therapy used to treat solid tumors, and the aging population as a whole, a respectable percentage of whom harbor known or as yet undiagnosed antecedent hematologic disorders. Case finding within this undiagnosed population will result in continued upward incidence trends.

Distinguishing biological characteristics

Compared to younger adults, older AML patients are more likely to have AML with poor-risk cytogenetics (such as abnormalities of chromosomes 5, 7, 8, or complex cytogenetics) and less likely to have good-risk cytogenetic findings, such as the balanced, core binding factor abnormalities, including the t(8;21) in which the *AML1-ETO* genes are juxtaposed, inv (16) and t(16;16) involving the CBFB-MYH11 chimeric product, and the PML-RARα mutation (t(15;17)).[3-7] Despite the overriding dismal prognostic implications of advanced age, cytogenetics still have relevance in predicting outcome, with fortunate older adults with leukemias typified by a CBF abnormality experiencing five-year overall survival rates of 20%, compared to 0% for those with poor-risk features.[8] Whether newly identified molecular lesions, such as FMS-like tyrosine kinases 3 (*flt3*) internal tandem duplications (ITDs) and mutations of nucleophosmin (NPM) play a role in older AML patients has yet to be determined.

Secondary AML, which is less responsive to chemotherapy, is also common in this age group, comprising between a quarter and half the cases, compared to < 10% in younger adults.[7,9] As a result, AML in older adults is more likely to arise from a more proximal stem cell disorder, and with abnormalities in more than one hematopoietic cell lineage.[1] Further chemotherapy responsiveness is mediated by greater expression of genes that confer drug resistance, such as MDR1, the P-glycoprotein (gp170) chemotherapy

efflux pump, present in one study in 71% of myeloblasts in older adults, compared to only 35% of blasts in younger AML patients.[11]

Poor outcome compared to younger adults

Older adults with AML have median and long-term survival rates comparable to patients with metastatic renal or lung cancer, even with the best available therapies. Younger adults with AML who receive standard remission induction therapy experience complete remission (CR) rates of 65-85%, a full 25% higher than all older adults, and at least 35% higher than the *very old*: patients 70 years or more.[9,12-17] As expected with lower CR rates, 5-year overall survival (OS) rates, which approach 30% in younger adults, are cut by half for older adults, and range from 5-15%.[14,18-20] This low chance of durable remission comes at a price of a high treatment-related mortality that approaches 25%, compared to less than 10% in the younger population. Morbidity may also be extreme, with many older adults without advanced directives requiring stays in intensive care units. Interestingly, age alone does not appear to predict successful outcome from an intensive care unit admission.

Why do older adults fare so much worse compared to younger AML patients? A simple answer is intolerance to remission induction therapy because of comorbid disease. More complicated reasons involve the biological factors described above; differential drug metabolism compared to younger adults, resulting in supratherapeutic drug levels, and the reluctance of many physicians to treat older adults intensively. Fewer than 40% of AML patients 65 years of age or older in the USA are treated with chemotherapy, and median survival among this population is 2.4 months. In summary, within older AML patients treated with remission induction therapy, approximately one-half will leave the hospital in a CR; one in 4 will leave with persistent disease; and one in 4 will not leave the hospital alive.

Treatment approaches in older adults are distinct

Deciding on intensive therapy for older adults

AML has traditionally been considered a medical emergency, with immediate initiation of therapy thought to be crucial to minimizing disease-related morbidity and mortality. Physicians must weigh the risks associated with giving immediate intensive therapy to patients in whom poor prognostic characteristics, such as advanced age and adverse cytogenetics, predict a low CR rate, with the risk of waiting to initiate treatment for additional test results to return. One study from the Cleveland and Houston groups exploring the effect of time from AML diagnosis to treatment on complete remission rates and overall survival in over 1,300 AML patients found that delaying therapy in older adults had no impact on these outcome parameters.[21] For younger adults, on the other hand, every day of delay predicted for lower CR and OS rates. Thus, older patients may benefit from waiting for the results of additional testing, allowing enrollment into studies that account for cytogenetic findings or that target molecular abnormalities.

Although indirect data support the use of intensive chemotherapy in older patients, most will derive little benefit from this approach. Only one randomized study, reported two decades ago, has ever shown a survival advantage (of only ten weeks) of remission induction therapy over low-dose therapy or best supportive care.[22] A more recent case-control study showed a survival advantage for giving intensive chemotherapy compared to best supportive care or low-dose approaches of 197 days vs. 53 days (HR 1.88, p=0.01).

The decision of whom to treat with intensive chemotherapy is difficult at best. In this issue of the journal, Malfuson and colleagues examined prognostic factors impacting the outcome of 416 older AML patients treated as part of the ALFA-9803 trial, using a regression model, to develop a decision index to identify older patients most likely to benefit from intensive chemotherapy.[23] Factors included in the index included high-risk cytogenetics, age ≥75 years, performance status ≥2, and white blood cell count ≥50,000/mL. The authors conclude that patients with a DI > 0 should not be treated with intensive chemotherapy, as their likelihood of being alive 12 months later was only 19%. This treatment decision should be incorporated into considerations of quality of life, which will suffer during hospitalization for remission induction therapy.[24]

Remission induction therapy

Once a decision has been made to initiate intensive chemotherapy, older AML patients are treated similarly to younger patients. The backbone of remission induction therapy consists of an anthracycline or anthracenedione combined with cytosine arabinoside (cytarabine, Ara-C), a regimen that has changed little since it was first introduced 30 years ago.[25,26] Typically, daunorubicin is given at a dose of 45 mg/m^2/d×3 days, or mitoxantrone or idarubicin are given at doses of 12 mg/m^2/d×3 days, in combination with cytarabine, which is administered as a continuous infusion at 100 or 200 mg/m^2/d×7 days (7+3 chemotherapy). While certain approaches, such as increasing the doses of cytarabine or the anthracycline, comparisons of different anthracycliness or anthracenedione, adding additional drugs, and/or using growth factors as priming agents or as supportive care[9,12,15,16,18,19,27] have variably improved CR rates and disease-free survival, they commonly come at the price of increased treatment-related mortality, thus offsetting any potential survival advantage. The median survival for older AML patients following these intensive approaches is typically 10-12 months, with higher median survival for those entering a CR, compared to non-responders or those achieving a CR with incomplete platelet recovery (CRi).

One potential improvement on the 7+3 mantra may be the addition of gemtuzumab ozogamicin. The Phase III MRC AML 15 trial compared cytarabine-based therapy + gemtuzumab to standard cytarabine-based induction therapy in 1,115 younger AML

patients.[28] Patients randomized to the gemtuzumab arm had a similar CR rate and rates of induction death and resistant disease compared to patients randomized to standard therapy, but higher disease-free survival at three years of follow-up (51% *vs.* 40%, p=0.008), with an indication that this will translate into improved OS. Whether similar improvements will be seen in older adults with AML has yet to be determined. FLT3 inhibitors are actively being studied in combination with traditional cytotoxic therapy, as has modulation of MDR, though conflicting results from large clinical trials have prevented the routine incorporation of MDR modulators into standard AML regimens.

Post-remission therapy

Standard post-remission approaches to therapy in older AML patients usually involve cytarabine administered for fewer days than in the remission induction setting, either alone or in combination with an anthracycline or anthracenedione, for 1-2 cycles. High doses of post-remission cytarabine have been associated with severe neurological toxicity in approximately one third of patients. No additional survival benefit is derived from more intensive post-remission therapy, adding other agents, or from maintenance therapy, though some data exist for a more protracted course of post-remission therapy.[14,19,20] Despite this recommendation, no randomized study has shown that, in older adults, some amount of post-remission therapy provides a survival advantage over no post-remission therapy. One small study even suggests there is no benefit to post-remission therapy.

More commonly, stem cell transplantation (SCT) is being considered as post-remission therapy. While SCT offers the chance of cure, it does so at the cost of high treatment-related mortality. SCTs have limited applicability to this population, due to comorbidities in recipients and in matched related donors, and to the limited availability of matched donors who are related to patients of an advanced age. Studies have demonstrated the feasibility of non-myeloablative approaches, with durable survival rates, and are ongoing. Ablative approaches have also been described in older AML patients, though may not provide any advantage over non-myeloabalative preparative regimens.[29,30]

Newer less-intensive treatment approaches

As there has been little headway in outcomes with older AML patients using intensive remission induction therapy, more contemporary trials have focused on less-intensive therapies that have the potential of effecting a complete remission while preserving quality of life.

Several novel cytotoxic agents are under investigation, with response rates that approach standard 7+3 induction regimens, though prospective comparisons to standard cytarabine-based intensive therapy have not been performed. Clofarabine is a purine nucleoside analog thought to inhibit ribonucleotide reductase, become incorporated into DNA; and induce apoptosis. In one study from the MRC, in which clofarabine was used as a single agent in newly diagnosed older adults,[31] the CR rate was 59%. This agent is now being explored in an oral form, and in combination with cytarabine. Cloretazine is an alkylating agent also being studied in older, *de novo* AML patients. One Phase II study including high-risk patients (such as older patients with poor-risk cytogenetics) demonstrated a CR rate of 28%. Improved outcomes were observed in those patients with *de novo* AML (50% CR) or intermediate-risk cytogenetics (39% CR). Both drugs are attempting to obtain US. Food and Drug Administration (FDA) approval for up-front treatment of AML in older adults. Tipifarnib, a farnesyl transferase inhibitor, has also been studied in clinical trials in older adults with AML. In a Phase II study of 148 evaluable, previously untreated older adults, the CR rate was 18% and the median overall survival was 5.6 months for all patients.[32] However, this drug has not been able to obtain US FDA approval.

Another approach is to take advantage of inhibiting the promoter hypermethylation of tumor suppressor genes thought to play a role in survival of AML cells. Two drugs, azacitidine and decitabine, have been studied in higher-risk MDS populations that included older adults wth AML. In the European AZA-001 study, azacitidine was compared to conventional care in 358 patients with advanced MDS, 33% of whom had 20% blasts or greater (considered AML by the WHO classification system). Response rates, including complete and partial remissions, were similar or better for azacitidine compared to standard induction chemotherapy, as was overall survival, though an important caveat is the subgroup nature of this comparison.[33] Decitabine was also studied in higher-risk MDS and AML patients by the Houston group and found to yield CR rates of 39%. A crucial point to interpreting these data is the importance of administering either of these drugs for prolonged periods of time; a median of 9 cycles for the AZA-001 study, and more than 5 cycles for the decitabine study.

Finally, an approach that should not be discounted, and perhaps should be considered the standard of care for less-intensive therapies in older adults, is low-dose cytarabine. When studied by the MRC, this drug resulted in a CR rate of 18% in older AML patients considered *not fit* for intensive chemotherapy, and demonstrated a significant survival advantage over hydroxyurea. Low-dose cytarabine is being combined with the anti-CD33 monoclonal antibody lintuzumab in an international Phase IIb trial in older adults in the up-front setting.

Conclusion

Older adults with AML represent one of the more challenging groups to treat in oncology, due to the refractoriness of the disease itself, the frailty of the population, and the imperative to incorporate quality of life issues into every treatment decision. Given the desperate nature of survival outcomes, clinical trials should be considered at diagnosis, along with considerations of aggressiveness of therapy and patient-oriented treatment goals.

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